Remarks

Claims 1-44 have been canceled. New claims 45-86 have been added.

Claim Rejections under 35 USC 112

In response to the rejection of the claims as failing to comply with the written description requirement, Applicants reiterate that, as argued in the previous Response, the term "prodrug" is well understood by those skilled in the art as evidenced by the previously submitted Exhibit A and in view of the description of "prodrugs of ambroxol" at page 11, lines 16-24 of the instant application. Nonetheless, Applicants have also submitted new claims 64-83 which delete the term prodrug from these claims. Thus, the rejection has been overcome by the arguments or the amendments set forth herein.

In response to the rejection based upon lack of enablement for treating the diseases listed in the claims, Applicants point out that the specification provides working examples demonstrating that a combination of α-lipoic acid, ambroxol and an inhibitor of angiotensin-converting enzyme promotes survival of neuronal cells after oxygen glucose deprivation (OGD) (see Examples 2 and 3). Applicants further submit attached hereto as Exhibit A supporting data for the present claims. The Figure shows the number of intact neurons in the CA1 hippocampus region in a global ischemia gerbil model. The animals were intrperitonealy injected with mixtures of amobroxol (ESP01), α-lipoic acid (LS) and elanopril (ACE), and NaCl as a control. For NaCl (n=33); ambroxol + α-lipoic acid + elanapril (n=7); ambroxol + α-lipoic acid (n= 11); ambroxol alone (n=7); "Schein-OP" = no ischemia. As can be seen, the combination of ambroxol + α-lipoic acid + elanapril, as well as the combination of ambroxol and α-lipoic acid, resulted in significant neuro protection. Therefore, one skilled in the art would understand that the presently claimed method would be effective at treating the presently recited neurodegenerative diseases. Applicants therefore respectfully request the Examiner to remove the stated rejection and allow the claims.

Claim rejections under 35 USC 103

The examiner has imposed a rejection under 35 USC 103(a) and has asserted that claims 1-6 and 16-17 are unpatentable over Gillissen et al., in further view of Derick et al. and Elena et al. The Examiner asserts that Applicant claims a composition for correcting a disturbance of thiol-disulfide status, and parenthetically references "correcting GSH deficiency."

In response, Applicants are unclear as to which claims the Examiner is referring in imposing this rejection. Specifically, the Examiner deems unpersuasive the Applicants' arguments purportedly filed November 10, 2005. However, the previous response for this application was filed on October 13, 2005. Moreover, none of the previously pending claims, nor the presently presented claims, recite correcting a disturbance of thiol-disulfide status or correcting GSH deficiency. Applicant has learned by inspection of public PAIR that a rejection of nearly identical phrasing was imposed by the Examiner against application serial no. 10/478,174 (in view of which the Examiner has also imposed a provisional double patenting rejection against the present application). Applicants respectfully suggest that the Examiner may be inadvertently addressing the claims of the '174 application in the current Office Action because the characterization of the present or previously pending claims as reciting a composition for correcting a disturbance of thiol-disulfide status is clearly erroneous. Nonetheless, Applicants address the cited references as follows.

The Examiner contends Gillissen et al. teach a composition comprising ambroxol as an anti-oxidant therapy and makes the conclusory statement that Gillissen et al. teach correcting a GSH deficiency.

In response, Applicants point out the anti-oxidant activity of ambroxol is described in Gillissen et al. only in the context of the pathology of lung disease. Ambroxol is not discussed with respect to modulating GSH levels. Further, GSH itself is only generally discussed in Gillissen et al. in respect of the well recognized glutathione redox cycle depicted in Figure 1 of Gillissen et al. What is more, Gillissen et al. state that ambroxol is capable of reducing oxidant-related cell damage through inhibition of phospholipases, stimulation of the lung surfactant system, inhibition of cytokines, and inhibition of chemotaxis response of neutrophils fMLP (see page 613, top of left column), but do not attribute correction of a GSH deficiency to ambroxol. Therefore, the

Examiner's conclusory assertion that ambroxol is described in this reference for use in correcting a GSH deficiency is unsupported by the cited reference. Moreover, while Gillissen et al. assess the effects of *N*-acetylecysteine and ambroxol in anti-oxidant therapy, Gillissen et al. fail to provide any teaching, suggestion or motivation even to combine the two anti-oxidants under direct investigation in this reference, let alone with angiotensin inhibitors or α-lipoic acid. Therefore, this reference does not teach, suggest or motivate the present invention in any way.

With respect to Elena et al., Applicant notes that this reference assesses the capability of elanapril and captopril to enhance glutathione-dependent antioxidant defenses. However, like Gillissen et al., these authors fail to test a combination of these compounds, and provide no teaching, suggestion or motivation to combine them with any other compounds. Therefore, this reference does not teach, suggest or motivate the present invention.

With respect to Derick et al., this reference also fails to provide any teaching, suggestion or motivation to combine α-liopic with other compounds having similar activity.

With respect to the Examiner's explanation of a motivation to combine the references, Applicants reiterate that Gillissen et al. does not teach correction of a GSH deficiency using ambroxol. Therefore, ambroxol cannot be said to be a compound that is known to perform the same function as an ACE inhibitor or α-lipoic acid. Therefore, it is incorrect to assert that the presently claimed compositions are prima facie obvious because the presently claimed compositions are a not a combination of compounds known to perform the same function individually.

Applicants also point out that, with respect to the holding of *In re Kerkhoven*, this decision did not defeat the long recognized patentability of a combination of known compounds when there is a showing of unexpected results when using the combination. Specifically, MPEP 716.02(a)I indicates that evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism") (citing Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). In this regard, Applicants point out the presently presented claims

include claims directed to obtaining a synergistic improvement in the survival of neuronal cells after oxygen and/or glucose deprivation comprising administering a composition comprising ambroxol, at least one inhibitor of the angiotensin-converting enzyme, and α-lipoic acid. Applicants have demonstrated this synergistic effect in Example 3. Moreover, in addition to demonstrating this synergistic effect, Applicants have shown that none of α-lipoic acid, ambroxol or elanapril, when applied alone, were capable of reducing neuronal damage after oxygen glucose deprivation (see page 9, line 21, through line 4, page 10). Therefore, this result is clearly surprising in view of the cited references. Applicants therefore submit that there is nothing in the cited references, either alone or in combination, that suggest, teach or motivate such a method.

With respect to the rejection of the claims as claiming the same invention as that of copending application serial nos. 10/478,174 and 10/4790,080, Applicant respectfully requests the Examiner to hold this rejection in abeyance until such time as the present application is otherwise deemed allowable.

Conclusion

Based on the arguments and amendments presented herein, Applicants believe all the pending claims are now in condition for allowance and respectfully request the Examiner to allow all the claims.

Applicants request a one-month extension of time to file this response. A check for the required fee of $120.00 is enclosed. Please charge any additional fees due or credit any overpayment to deposit account number 08-2442.

Respectfully submitted,
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EXHIBIT A